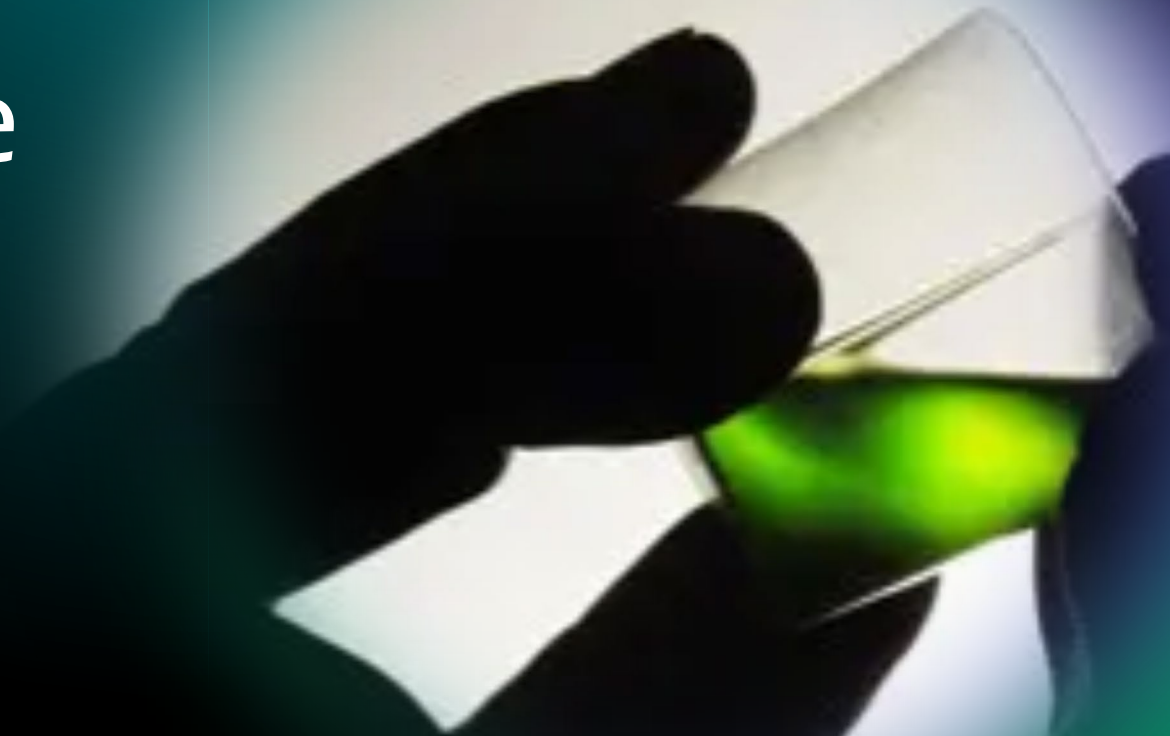


Is methadone use contraindicated in people who use SCRAAs?

DR CAROLINE COPELAND

LECTURER IN PHARMACEUTICAL MEDICINE,
KING'S COLLEGE LONDON

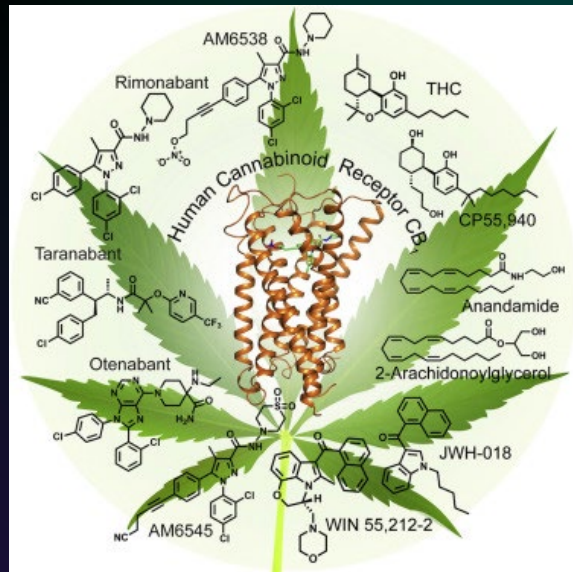
DIRECTOR, NATIONAL PROGRAMME ON
SUBSTANCE ABUSE DEATHS



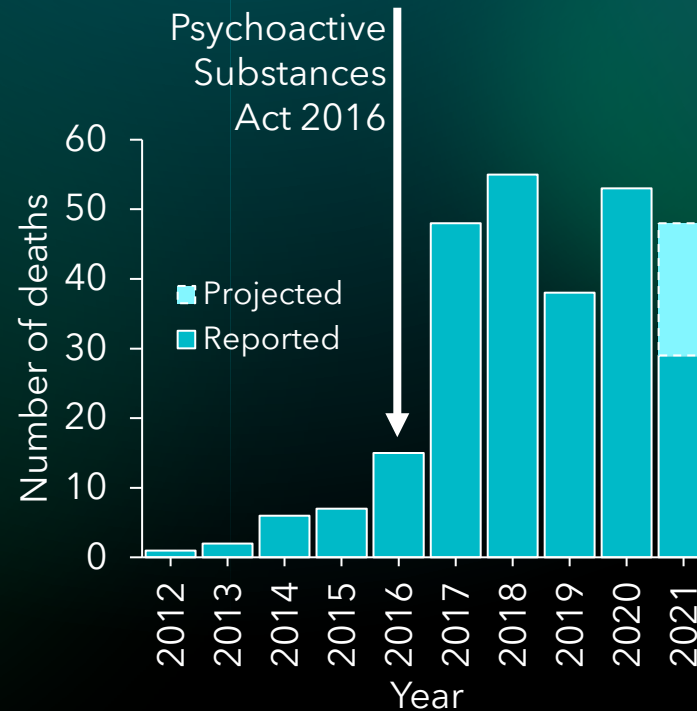
YES

(well, probably...)

Synthetic cannabinoid receptor agonists (SCRAs & 'Spice')



Potent CB₁ receptor agonists



On average ~50 deaths a year in England, Wales & Northern Ireland since 2017¹

Original Paper

Deaths from novel psychoactive substances in England, Wales and Northern Ireland: Evaluating the impact of the UK psychoactive substances act 2016

Adrian A Deen¹, Hugh Claridge², Richard D Treble³, Hilary J Hamnett⁴ and Caroline S Copeland^{1,2}

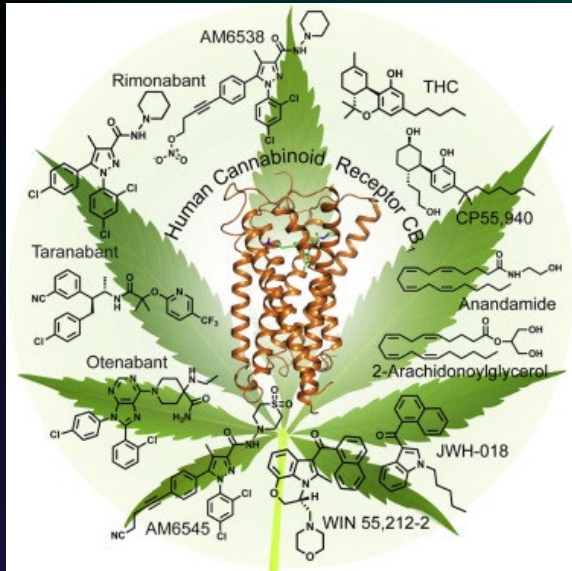
Journal of Psychopharmacology
1-9
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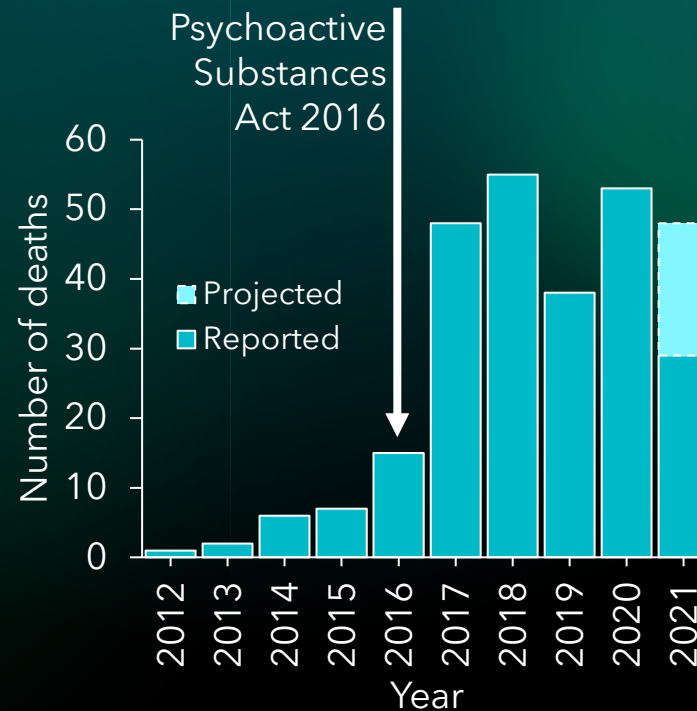
SAGE

1. National Programme on Substance Abuse Deaths, 2022
2. Yoganathan et al., 2022, Cannabis and Cannabinoid Research 7:516-525

Synthetic cannabinoid receptor agonists (SCRAs & 'Spice')



Potent CB₁ receptor agonists



On average ~50 deaths a year in England, Wales & Northern Ireland since 2017¹



Polydrug use in 90.3%² of cases

Are most SCRA users polydrug users?

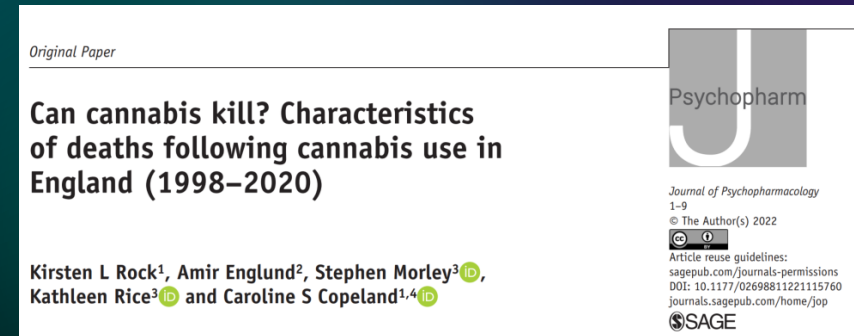
OR

Does SCRA use alone have limited risk of fatality?

1. National Programme on Substance Abuse Deaths, 2022
 2. Yoganathan et al., 2022, Cannabis and Cannabinoid Research 7:516-525

Mechanism of fatal toxicity?

- Cannabis toxicity n=1/3,455 cases
- SCRA toxicity?
 - Cardiac pathophysiology?¹
 - 'Sudden collapse' in 81.6% of witnessed deaths¹



Cause	Immediate cause % of Decedents (n)	Underlying cause % of Decedents (n)
Acute drug use	67.3 (111)	87.9 (145)
Implicating SCRA(s)	57.6 (95)	75.8 (125)
Not implicating SCRA(s)	9.7 (16)	12.1 (20)
Physiological system	32.7 (54)	12.1 (20)
Cardiac	10.3 (17)	7.3 (12)
Respiratory	13.3 (22)	6.1 (10)
Neurological	9.1 (15)	3.6 (6)
Hepatic	1.2 (2)	1.8 (3)
Mental health	0.6 (1)	0.6 (1)
Gastrointestinal	0.6 (1)	—
Trauma	—	—
Other	3.0 (5)	3.0 (5)

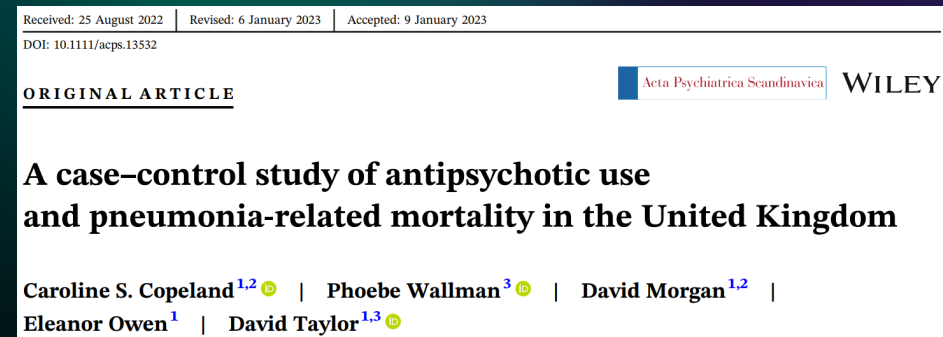
1. Yoganathan et al., 2022, Cannabis and Cannabinoid Research 7:516-525

Sudden Cardiac Death?

Cases with post-mortem detections of SCRA were extracted from the National Programme on Substance Abuse Deaths (NPSAD) & screened for type of drug(s) co-detected

National Programme on Substance Abuse Deaths (NPSAD)

- Over 25 years of data on deaths following psychoactive drug use (since 1997)
 - Illicit drugs (e.g., SCRAs, LSD, cocaine)
 - Licensed medications (e.g., antidepressants, antipsychotics)



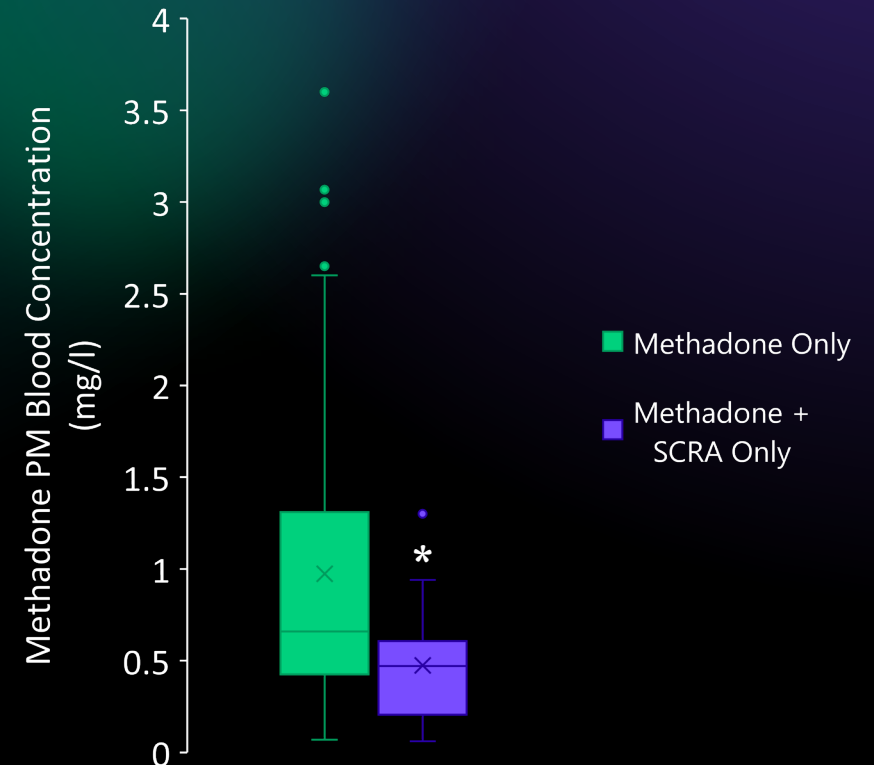
- ~50,000 individual case reports
 - Decedent demographics (sex, age, ethnicity, living arrangements, employment status, usual address)
 - Details pertaining to death (cause[s] of death, toxicology, circumstances of death, place of death)
 - History (prescribed medications, in contact with services [mental health, drug & alcohol])
- Interested? caroline.copeland@kcl.ac.uk

Sudden Cardiac Death?

Cases with post-mortem detections of SCRA(s) were extracted from the National Programme on Substance Abuse Deaths (NPSAD) & screened for type of drug(s) co-detected

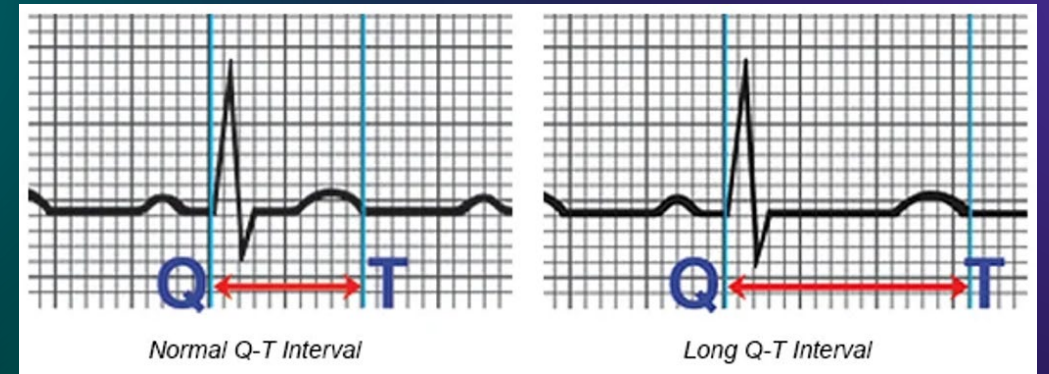
Substance detected	No. of cases	Percent
Only SCRA(s)	14	5.5%
SCRA and medications with long QT liability	26	10.2%
SCRA and non-medical drug with cardiac effect	76	29.9%
SCRA, medication with long QT interval liability and non-medical drug with cardiac effect	121	47.6%
SCRA and other drug(s) with no known cardiac effects	17	6.7%

} 87.7%

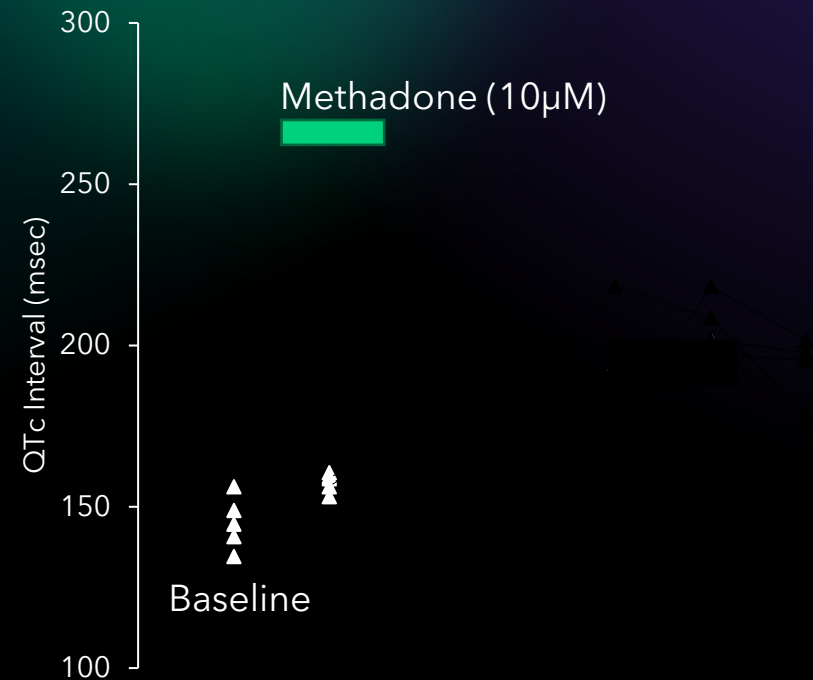


Long QT Liability?

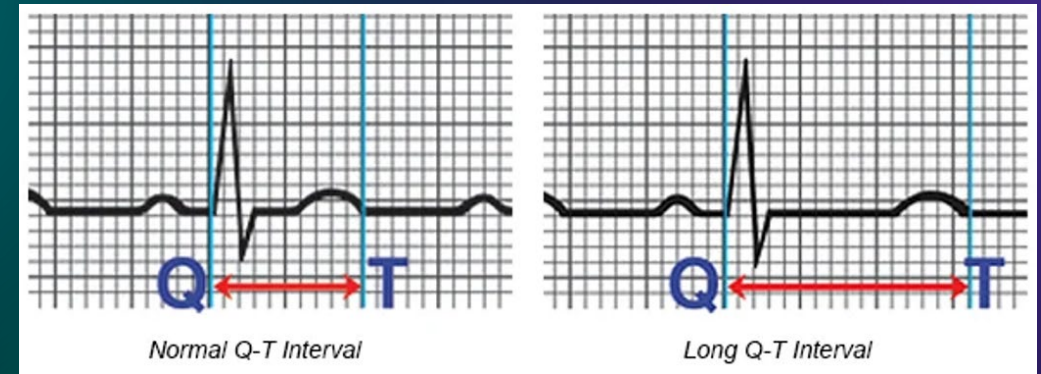
- Guinea-pig hearts (n=6) were perfused (Langendorff mode) and cardiac electroencephalogram (ECG) recorded
- 10uM methadone increased QT interval by ~10msec



Can lead to Torsades de Pointes

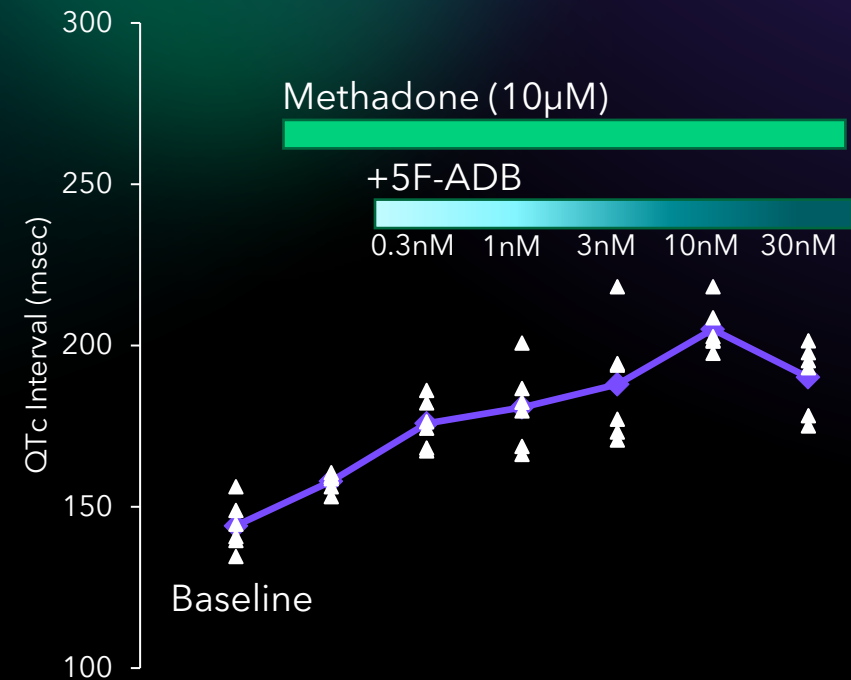


Long QT Liability?



Can lead to Torsades de Pointes

- Guinea-pig hearts (n=6) were perfused (Langendorff mode) and cardiac electroencephalogram (ECG) recorded
- 10uM methadone increased QT interval by ~10msec
- Co-application of 5F-ADB had a dose-dependent effect on increasing QT interval by up to ~50msec
- 5F-ADB alone had no effect on QT interval



Is methadone use contraindicated in people who use SCRAs?

- **Yes** (well, probably.....)
 - Need to test with other (newer) SCRAs
- What about other medications with long QT liability?
 - Quetiapine, citalopram etc.
- What is a realistic recommendation?
 - Buprenorphine?
 - Promote awareness of the drug-drug interaction?

Thanks to....

NPSAD

Kirsten Rock



Shouqi Chen



LGC

Simon Hudson



Cardiovascular Sciences

Louise Hesketh



Mike Shattock



Mike Curtis



Any Questions?